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Systemic sensitivity to corticosteroids in smokers with asthma

E. Livingston*, R. Chaudhuri*, A.D. McMahon[¶], I. Fraser[#], C.P. McSharry[#] and N.C. Thomson*

ABSTRACT: Cigarette smokers with asthma are insensitive to the therapeutic effects of corticosteroids. It is not known whether this insensitivity to corticosteroids in smokers affects tissue sites beyond the airways.

A total of 75 asthmatic subjects (39 smokers) and 78 healthy controls (30 smokers) were recruited to an observational study. The cutaneous and peripheral blood lymphocyte responses to corticosteroids were measured. The cutaneous vasoconstrictor response to topical beclometasone was measured by applying different concentrations of beclometasone solutions to the skin in a random double-blind manner. The degree of blanching at each concentration was graded after 18 h. The sensitivity of peripheral blood lymphocytes to corticosteroids was assessed by measuring the suppressive effect of dexamethasone on lymphocyte proliferation stimulated by phytohaemagglutinin (PHA).

Total mean±SD cutaneous vasoconstrictor response score to beclometasone was reduced in smokers with asthma to 5.39±3.58 *versus* 7.26±3.05 in never-smokers with asthma; and in all smokers to 6.47±3.33 *versus* 7.86±2.81 in all never-smokers. The sensitivity to corticosteroids of lymphocytes stimulated by PHA was similar between groups.

In conclusion, smokers with asthma have an impaired cutaneous vasoconstrictor response to topical corticosteroids compared with never-smokers with asthma. This finding suggests that the insensitivity to corticosteroids in smokers with asthma affects tissue sites other than the airways.

KEYWORDS: Asthma, corticosteroid insensitivity, cutaneous vasoconstriction, lymphocyte proliferation, smoking

Corticosteroids are the most effective anti-inflammatory therapy currently available for the treatment of asthma and are recommended in international guidelines [1]. A subgroup of asthmatics do not obtain an adequate therapeutic response to corticosteroids and are termed corticosteroid resistant or insensitive [2]. The causes of corticosteroid-insensitive asthma are considered to be multifactorial, involving both genetic and environmental factors [2, 3] including cigarette smoke [4]. Cigarette smokers, compared with never-smokers, with asthma are less sensitive to both inhaled [5, 6] and oral corticosteroids [7] as assessed by changes in lung function and asthma symptoms. Smokers with asthma account for >20% of adults with asthma [4] and compared with never-smokers experience more severe asthma symptoms [8] and accelerated decline in lung function [9].

It is not known whether smokers with asthma are insensitive to corticosteroids in tissue sites other than the airways. The cutaneous vasoconstrictor response to topical beclometasone [10, 11] and the ability of corticosteroids to inhibit the activation of peripheral blood lymphocytes [12] have been used as an index of systemic sensitivity to corticosteroids. Never-smokers with corticosteroid-insensitive asthma have impaired cutaneous vasoconstrictor responses to corticosteroids [13] and the inhibitory effect of corticosteroids on lymphocyte proliferation is reduced [12]. The present authors hypothesised that smokers with asthma have reduced corticosteroid sensitivity in sites other than the lungs. The aim of the present study was to compare systemic sensitivity to corticosteroids in smokers and never-smokers with and without asthma by assessing the cutaneous vasoconstrictor response to topical beclometasone and the sensitivity of stimulated lymphocytes to corticosteroids.

MATERIALS AND METHODS

Subjects

Smoking and never-smoking subjects with and without asthma (white and non-white people) aged 18–60 yrs were recruited from hospital

AFFILIATIONS
Depts of *Respiratory Medicine, and [#]Immunology, University of Glasgow, and [¶]Robertson Centre for Biostatistics, Glasgow, UK.

CORRESPONDENCE
N.C. Thomson
Dept of Respiratory Medicine
Division of Immunology
Infection and Inflammation
University of Glasgow and
Western Infirmary
Glasgow
G11 6NT
UK
Fax: 44 1412113464
E-mail: n.c.thomson@clinmed.gla.ac.uk

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outpatient clinics and hospital staff, respectively. All participants gave written informed consent and approval for the study was obtained from the West Glasgow Ethics Committee (Glasgow, UK). Asthma was diagnosed by American Thoracic Society (ATS) criteria [14] and all asthmatic subjects had a baseline forced expiratory volume in one second (FEV1) $\leqslant$85% predicted and a reversibility of FEV1 after nebulised salbutamol of $\geqslant$15%. Exclusion criteria were asthma exacerbations, use of oral corticosteroids or a respiratory tract infection within 4 weeks of inclusion. Healthy volunteers had no history of respiratory disease. Smokers had smoked $\geqslant$10 pack-yrs and were currently smoking $\geqslant$10 cigarettes·day^{-1}. A total of 35 asthmatic subjects (19 smokers) were also taking long-acting β_2-agonists; three asthmatics (two smokers) were taking leukotriene receptor antagonists.

Study design

The current authors carried out an observational study in which the cutaneous, peripheral blood lymphocyte and airway responses to corticosteroids were measured. Venous blood was collected for lymphocyte responses, total and specific serum immunoglobulin (Ig)E levels and serum cotinine levels. The cutaneous vasoconstrictor response to topical beclometasone was measured on the same day by applying beclometasone solutions to the skin in a random double-blind manner and assessing the degree of blanching. Sputum induction was performed in subjects with asthma and fractional exhaled nitric oxide ($F_{E}NO$) and carbon monoxide were measured in all subjects. Subjects with asthma received 40 mg of oral prednisolone daily for 14 days. The end-points used to assess airway corticosteroid sensitivity were change in morning and evening peak expiratory flow (PEF) rate, pre-salbutamol FEV1, validated asthma control score, daily morning and night symptoms and a reduction in the use of rescue inhalers.

Measurements

Baseline measurements and diary card recordings

Asthma severity was scored at baseline using the ATS asthma impairment score [15] and asthma control was scored at each visit using a validated asthma control questionnaire [16]. Patients maintained a validated home diary card [17] recording morning and night PEF, daytime symptoms (range 0–6, for increasing severity) and night awakenings (range 0–3, for increasing severity), use of inhaled rescue medication and study tablet consumption. Compliance was assessed by tablet count. Asthma duration was determined from patient clinical history and hospital records when available. Total serum IgE and specific IgE to house dust mite, grass pollen and cat dander were measured by enzyme linked immunoassay (Unicap; Pharmacia Ltd, Milton Keynes, UK). Total IgE level $>$120 IU·mL^{-1} and specific IgE $>$0.35 IU·mL^{-1} were considered elevated. A subject was defined as nonatopic when specific IgE to all common allergens was negative [18]. Serum cotinine was measured using an enzyme immunoassay (Cozart Bioscience Ltd, Abingdon, UK) as confirmation of smoking status.

Lung function testing, sputum induction and exhaled gases

Spirometry was measured with a dry spirometer (Vitalograph Ltd, Buckingham, UK) and the best of three attempts was taken for analysis. FEV1 was measured before and 15 min after administration of 2.5 mg nebulised salbutamol. Sputum induction with 3% hypertonic saline was performed using a modification of the method described by PIN *et al.* [19]. The sputum was processed and the dispersed cell total and differential count obtained using the technique described by POPOV *et al.* [20]. Subjects were requested not to smoke for 1 h prior to their visits and $F_{E}NO$ was measured using a chemiluminescence analyser (LR2000; Logan Research Ltd, Rochester, UK), with a detection limit of 0.1 ppb NO. NO levels were taken from the plateau at the end of exhalation and the mean of triplicate measurements was used as the representative value [21].

Cutaneous vasoconstrictor response to topical beclometasone

The cutaneous vasoconstrictor response to topical beclometasone was measured as described previously [10], with minor modifications. Beclometasone dipropionate (Sigma-Aldrich, Gillingham, UK) was dissolved in 95% ethanol to concentrations of 1, 3, 10, 30, 100, 300 and 1,000 μg·mL^{-1}. A control solution of 95% ethanol was used. Test sites were outlined on the nondominant flexor forearm by the application of adhesive tape in which 2-cm diameter holes had been cut. Solutions were randomly allocated a letter (A–H) by staff not involved in the application or reading of the test and solutions applied in order A–H. The test was not unblinded until the completion of the study. The sites were occluded with plastic film to enhance percutaneous absorption of the beclometasone. A tubular bandage (Tubigrip; Seton Healthcare Group, Oldham, UK) was applied to attenuate any changes in ambient temperature. After 18 h, the tape and film were removed and the degree of blanching assessed after a further 1 h. The test sites were examined in standard lighting conditions and given a blanching score by a single trained observer. Blanching at each concentration was graded according to a four-point scale: 0=no blanching; 1=faint blanching; 2=obvious blanching not extending beyond the test site; and 3=intense blanching extending over the margin of the test site. The addition of individual concentration scores gave a total score. A high score indicates a high degree of corticosteroid sensitivity.

Lymphocyte proliferation response

The sensitivity of peripheral blood mononuclear cells (PBMCs) to corticosteroids was assessed in a functional assay as described previously [12]. PBMCs were separated from whole blood using Lymphoprep (Axis-Shield PoC AS, Oslo, Norway). Cells were then resuspended at 1×10^6 lymphocytes·mL^{-1} in RPMI 1640 medium supplemented with 10% foetal calf serum, 1.25 μg·mL^{-1} fungizone, 1% L-glutamine, 100 μg·mL^{-1} penicillin and 100 IU·mL^{-1} streptomycin. Cell viability was assessed by trypan blue exclusion and was always $>$95%. PBMCs were incubated in triplicate at a concentration of 1×10^5 cells·100 μL^{-1}·well^{-1} in 96-well round-bottomed plates (Iwaki microplates; Bibby Sterilin, Stone, UK). The T-lymphocyte mitogen phytohaemagglutinin (PHA; Biostat Ltd, Stockport, UK) was added to the cultured cells at a concentration of 0.6 μg·well^{-1} after pilot studies (n=21 patients) had established that the suppressive effect of dexamethasone was almost independent of the amount of PHA used over the range 0.054–0.6 μg·well^{-1}. Dexamethasone (Sigma-Aldrich; 10^{-11}–10^{-4} M final concentration) was added and the plates cultured at 37° C in a humidified atmosphere

with 5% CO_2 for 48 h. Cell proliferation was measured by uptake of tritiated thymidine. Results were expressed as counts·min^{-1}. Thymidine incorporation as an index of cell proliferation was compared between PHA-stimulated T-lymphocytes with or without dexamethasone. The percentage suppression at the final concentration of dexamethasone (defined as the maximum inhibition (I_{max}) for the present study) and the gradient of suppression at all concentrations of dexamethasone were compared between smokers and never-smokers with and without asthma.

Statistical analysis

Baseline characteristics were compared using Chi-squared tests and Wilcoxon tests. The effect of asthma and smoking upon the total skin-test score was assessed by ANOVA, including a test of interaction between the two factors. The responses to oral prednisolone of smokers *versus* never-smokers with asthma were assessed by ANCOVA models that adjusted each factor by its baseline measure. For those measurements taken from diary cards, the mean of days 1 and 2 was taken to be the baseline and the mean of days 11–14 was taken to be the response measurement. Spearman rank correlations were used to assess the strength of association between the total skin-test score and the various factors of interest. For each patient separately, the downward slope of the best-fitting line was calculated by linear regression. Lymphocyte proliferation response data are shown graphically as mean±SEM for clarity.

RESULTS

Baseline characteristics

There were no significant differences in the following: age; duration of asthma; equivalent dose of inhaled beclometasone; % pred baseline, pre- and post-bronchodilator FEV1; pre- and post-bronchodilator FEV1/forced vital capacity (FVC) ratio; reversibility (%) to inhaled salbutamol; ATS asthma impairment score; total IgE levels; and induced sputum percentage macrophage, neutrophil and lymphocyte counts among smokers and never-smokers with asthma (tables 1 and 2). Compared with never-smokers with asthma, the group of smokers with asthma contained fewer male subjects and had the following: lower absolute baseline FEV1; lower absolute reversibility to salbutamol; higher asthma control score; lower percentage testing positive for specific IgEs; and lower F_{ENO} levels (tables 1 and 2). Compared with healthy never-smokers, healthy smokers were older and had lower FEV1 (absolute and % pred) and lower pre-bronchodilator FEV1/FVC ratios. Smoking history was longer and the serum cotinine level was lower in asthmatic smokers *versus* healthy smokers (table 1).

Cutaneous vasoconstrictor response to topical beclometasone

There was a significant difference in the mean±SD total cutaneous vasoconstrictor response score between smokers (5.39±3.58) and never-smokers (7.26±3.05) with asthma ($p=0.023$; fig. 1); between all smokers (6.47±3.33) and all never-smokers (7.86±2.81; $p=0.006$); and between all asthmatics (6.29±3.44) and all controls (8.13±2.50; $p<0.001$). There was no difference between smoking (7.83±2.42) and never-smoking (8.33±2.56) controls ($p=0.228$; fig. 1). When adjusted for each other's effects, asthma ($p<0.001$) and smoking ($p=0.017$) are both independently associated with the cutaneous vasoconstrictor response. The mean (95% confidence interval (CI)) reduction for asthmatics after adjustment for smoking was -1.70 (-2.66– -0.73). Similarly, the mean

TABLE 1 Baseline demography of asthmatic subjects and healthy controls

	Asthmatic			Healthy controls		
	Smokers	Never-smokers	p-value	Smokers	Never-smokers	p-value
Subjects n	39	36		30	48	
Age yrs	47.4±7.4	45.1±10.9	0.42	39.9±8.6	35.2±8.0	0.029
Male n	20	29	0.008	10	17	0.85
Asthma duration yrs	21.7±15.7	28.9±17.2	0.07			
Smoking history pack-yrs	37.7±17.2***			22.8±14.9		
Cigarettes·day^{-1}	22.6±7.5*			19.3±7.1		
Smoking history yrs	30.6±7.2***			23.3±8.6		
Equivalent dose of inhaled beclometasone μg	997±905	631±646	0.11			
FEV1 L	1.95±0.70	2.26±0.77	0.045	2.84±0.81	3.35±0.93	0.014
FEV1 % pred	63.3±13.9	63.6±17.5	0.70	93.4±12.5	99.7±13.9	0.039
FEV1 post-salbutamol % pred	77.5±5.5	82.6±6.4	0.44			
FEV1/FVC pre-salbutamol	61.7±11.4	60.9±14.1	0.98	77.5±5.5	82.6±6.4	<0.001
FEV1/FVC post-salbutamol	65.0±12.1	64.8±15.2	0.77			
Reversibility to salbutamol %	22.7±11.4	25.6±11.9	0.23			
Reversibility to salbutamol mL	426±236	549±269	0.014			
ATS impairment score	5.1±1.9	5.2±1.9	0.829			
Asthma control score	2.66±1.08	1.67±0.83	<0.001			

Data are presented as mean±SD, unless otherwise stated. FEV1: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity; ATS: American Thoracic Society. *: $p<0.05$, smokers with asthma *versus* healthy smokers; ***: $p<0.001$, smokers with asthma *versus* healthy smokers.

TABLE 2 Allergy levels, serum cotinine, exhaled gases and induced sputum cell counts at baseline in asthmatic subjects and healthy controls

	Asthmatic			Healthy controls		
	Smokers	Never-smokers	p-value	Smokers	Never-smokers	p-value
Subjects n	39	36		30	48	
Total IgE IU·mL^{-1}	87 (41–239)	138 (60–590)	0.12	47 (13–74)	32 (14–111)	0.82
Specific IgE positive %	62	91	0.004	29	46	0.13
Serum cotinine ng·mL^{-1}	304 (131–375)*	2.6 (2–3)	<0.001	366 (310–421)	2.6 (2.3–3.8)	<0.001
Exhaled CO ppm	22 (16–30)	4.3 (4–5)	<0.001	18.42 (14.2–22.4)	3.79 (3.2–4.16)	<0.001
Exhaled NO ppb	5.1 (2.6–7.8)	18.2 (12.5–28.6)	<0.001	4.3 (2.9–8.1)	7.4 (5.6–8.7)	0.006
Induced sputum cell counts						
Macrophages %	50 (24–67)	51 (26–67)	0.93			
Neutrophils %	42 (23–66)	31 (13–44)	0.07			
Eosinophils %	1.0 (0.5–2.7)	2.0 (0.5–5.5)	0.51			
Lymphocytes %	1.7 (1–2.6)	2.5 (0.9–4)	0.61			
Bronchial epithelial cells %	2.6 (0.9–6.6)	5.8 (3.5–9.4)	0.020			

Data are presented as median (interquartile range), unless otherwise stated. Ig: immunoglobulin; CO: carbon monoxide; NO: nitric oxide. *: p<0.05, asthmatic *versus* healthy smokers.

(95% CI) reduction for smoking after adjustment for asthma was -1.18 (-2.15– -0.21). However, there is no evidence of synergy between the two variables (test of interaction, p=0.162).

Lymphocyte proliferation response

Dexamethasone had a concentration-dependent inhibitory effect on the proliferative response to PHA, which was similar in smokers compared with never-smokers, in asthma and in healthy controls (fig. 2). The mean±SD Imax was similar between smokers with asthma (50.3±26.5) compared with never-smokers with asthma (56±25.9) and in healthy controls who were smokers (60.8±21.1) compared with never-smokers (50.4±27.4; comparing all four groups p=0.29). The gradients of suppression at all concentrations of dexamethasone were similar in the four groups (p=0.44).

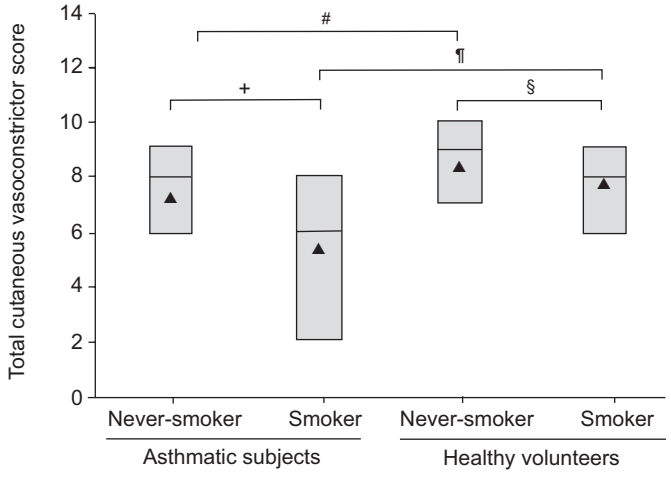

FIGURE 1. Cutaneous vasoconstrictor response to topical beclometasone in asthmatic subjects and healthy controls according to smoking status. ▭: interquartile range; ——: median; ▲: mean. #: p=0.091; ¶: p=0.003; +: p=0.023; §: p=0.224.

Airway response to oral prednisolone

After administration of high-dose oral corticosteroids, there was a significant improvement in mean (95% CI) morning PEF (26.2 (2.5–50); p=0.031), daytime symptoms (-2.3 (-4– -0.4); p=0.016), asthma control score (-0.9 (-1.4– -0.4); p=0.001) and rescue medication use (-0.8 (-1.5– -0.1); p=0.029) and a fall in F_{ENO} (3.2 (0.1–6.4); p=0.043) in never-smokers with asthma compared with smokers with asthma. There was no significant difference in the change in other end-points between the two groups (table 3).

Relationships between cutaneous vasoconstrictor response and baseline measurements

An increased number of cigarettes smoked per day was associated with a lower total skin-test score (r=-0.41; p=0.010), hence increased resistance to corticosteroids. The cutaneous vasoconstrictor response of the whole asthmatic population correlated negatively with the dose of beclometasone (r=-0.38; p<0.001) and asthma control score (r=-0.41; p<0.001), but there was no correlation with age (r=-0.175; p=0.139), duration of asthma (r=-0.08; p=0.491), asthma severity score (r=-0.17; p=0.154) or total IgE (r=-0.108; p=0.408).

DISCUSSION

The present study has demonstrated that the cutaneous vasoconstrictor response to topical beclometasone is reduced in smokers with asthma compared with never-smokers with asthma and smokers without asthma. These findings suggest, for the first time, that corticosteroid insensitivity in smokers with asthma may be more generalised, affecting tissue sites other than the airways.

The cutaneous vasoconstrictor response to topical beclometasone [10, 11] has been used as a screening test to determine the relative anti-inflammatory potency of corticosteroids [22] and as an index of systemic sensitivity to corticosteroids [13]. More objective methods of detecting glucocorticoid-induced skin blanching have been compared with the visual scoring system,

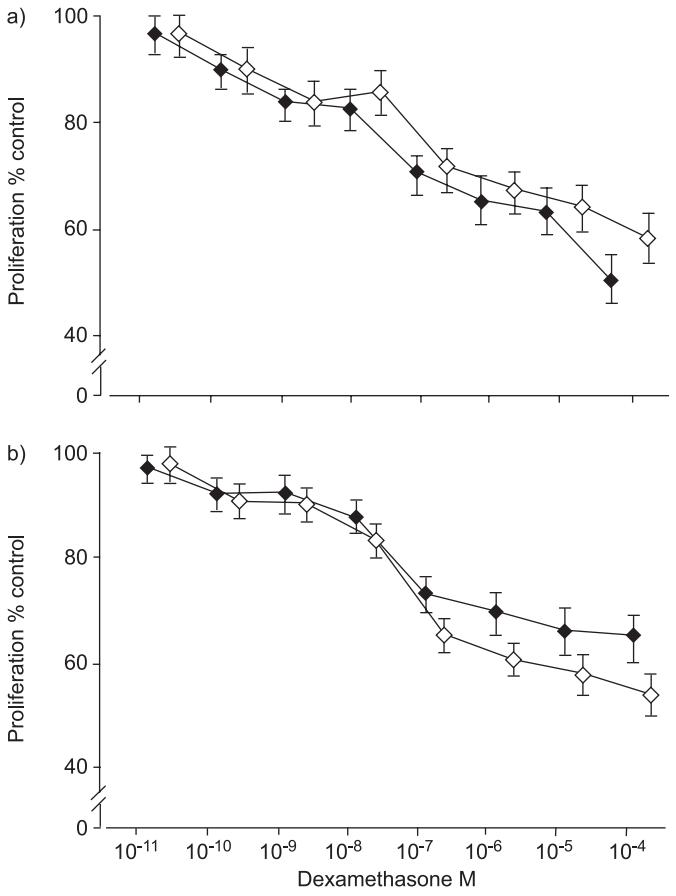

FIGURE 2. Inhibition of phytohaemagglutinin-induced proliferation of peripheral blood T-lymphocytes by dexamethasone (10^{-11}–10^{-4} M) from a) subjects with asthma and b) healthy controls. ♦: smokers; ◇: never-smokers. Data are presented as mean ± SEM proliferation in the presence of dexamethasone expressed as a percentage of that obtained without dexamethasone.

but the human eye has been found to be the most sensitive tool to measure dermal blanching [11]. The present authors found that smoking and asthma were independently associated with an impaired cutaneous vasoconstrictor response to topical beclometasone. These findings suggest that smoking and asthma acted in an additive manner to impair cutaneous vasoconstrictor responses. The reason(s) for the reduced cutaneous vasoconstrictor response in smokers with asthma is not clear. If chronic cigarette smoking were to alter the structure or function of skin microvasculature then this might influence the cutaneous vasoconstrictor response to corticosteroids. However, dermal thickness and elasticity of the forearm of smokers are similar to never-smokers [23] as is the cutaneous vasodilator response to intradermal histamine [24]. The dosage of inhaled corticosteroids, age, duration of asthma and severity score were similar between the smokers with asthma and the never-smokers with asthma, despite the former group showing impaired skin responses. The cutaneous vasoconstrictor response is inhibited by glucocorticoid receptor antagonist [25] and correlates with glucocorticoid receptor affinity [22]; the intensity of blanching is potentiated by inhibitors of the local metabolism of cortisol [26]. These findings suggest that the cutaneous vasoconstrictor response is likely to be mediated by glucocorticoid receptors. The negative correlation between the cutaneous vasoconstrictor response and the number of cigarettes smoked per day strengthens the evidence that smoking impairs the response to corticosteroids. It is unclear why asthma should be independently associated with an impaired cutaneous vasoconstrictor response to topical beclometasone. Corticosteroid use is associated with the downregulation of glucocorticoid receptors [27, 28] and, as most of the asthmatics were on a moderate dose of inhaled corticosteroids, this may be one explanation of why asthma appeared to be an independent risk factor for an impaired response.

The mechanisms by which corticosteroids cause vasoconstriction may involve inhibition in the uptake of the vasoconstrictor noradrenaline at nerve endings in the skin [29]. Exposure of human skin vasculature to nicotine potentiates noradrenaline-induced skin vasoconstriction [30], but whether nicotine or other constituents of cigarette smoke influence the vasoconstrictor response to corticosteroids is not known. The *in vivo* sensitivity to topical budesonide of healthy subjects is influenced by glucocorticoid receptor polymorphisms [31]. The glucocorticoid receptor α:β ratio is reduced in the PBMCs of cigarette smokers [32] and similar changes might affect glucocorticoid receptors in the skin. Other possible mechanisms of cigarette smoke-induced corticosteroid resistance implicated in other tissues [4], including reduced histone deacetylase (HDAC) activity [33], might be relevant to the skin. HDAC activity has shown to be reduced in patients with asthma [34], chronic obstructive pulmonary disease (COPD) [35] and in subjects who smoke [33]. A preliminary report suggests that HDAC activity is reduced in bronchial biopsies from asthmatic smokers compared with healthy smokers and asthmatic nonsmokers [36]. If similar changes in HDAC activity are found in the skin, this may explain the current findings. Taken together, the current findings suggest that corticosteroid insensitivity in smokers with asthma affects not only the airways but is also a systemic effect, as shown by the reduced, cutaneous vasoconstrictor response in smokers with asthma.

Cigarette smoking has been reported to increase [37] and to decrease [38] lymphocyte proliferation. This anomaly has been partly resolved in animal models by showing that acute tobacco smoke exposure or administration of nicotine is stimulatory for lymphocyte proliferation, whereas chronic exposure is inhibitory [39, 40]. A similar, approximately linear, dose-dependent level of sensitivity to corticosteroids was found in PHA-stimulated peripheral blood lymphocytes from smokers with asthma compared with never-smokers with asthma. This, in contrast to the impaired cutaneous vasoconstrictor response to topical beclometasone and reduced airway response to prednisolone in the former group, suggests variation in tissue sensitivity to corticosteroids in smokers with asthma. The reason(s) for the different tissue sensitivity in smokers is not known, but a lack of correlation between different tests of tissue sensitivity to corticosteroids has been reported previously in healthy volunteers [41]. As the lymphocyte proliferation test is performed *ex vivo*, it is possible that any effect of cigarette smoking on lymphocyte function may no longer be present. However, PBMCs from smokers have shown a reduced HDAC activity [33] and altered cytokine levels [42] *in vitro*.

TABLE 3 Response of lung function, symptoms, asthma control score and exhaled gases to high-dose[#] oral prednisolone in never-smokers with asthma and smokers with asthma

	Asthmatic		Difference	p-value
	Never-smokers	Smokers		
Subjects n	39	36		
Δ Morning PEF L·min^{-1}	20.4±50.1	6.3±44.8	26.2 (2.5–50)	0.031
Δ Night PEF L·min^{-1}	9.1±44.1	14.6±46.1	2.3 (-21–26)	0.84
Δ Pre-salbutamol FEV1 mL	165±390	85±303	98 (-71–266)	0.25
Δ Post-salbutamol FEV1 mL	8±436	-81±195	126 (-38–290)	0.13
Δ Reversibility with salbutamol %	-9.3±13	-10.5±14	3.0 (-2.8–6.8)	0.25
Δ Daytime symptoms	-1.8±3.1	-0.8±4.9	-2.3 (-4– -0.4)	0.016
Δ Night-time symptoms	-0.1±0.4	-0.2±0.9	-0.2 (-0.5–0.1)	0.12
Δ Rescue medication use	-0.7±1.3	-0.1±1.6	-0.8 (-1.5– -0.1)	0.029
Δ Asthma control score	-0.46±0.84	-0.31±1.25	-0.9 (-1.4– -0.4)	0.001
Δ Exhaled NO ppb	-12.4±15.1	-2.6±8.4	3.2 (0.1–6.4)	0.043
Δ Exhaled CO ppm	0.2±2.8	-0.9±8.8	-5.5 (-10– -0.7)	0.025

Data are presented as mean±SD and mean (95% confidence interval), unless otherwise stated. All variables have been analysed by ANCOVA. Δ: change; PEF: peak expiratory flow; FEV1: forced expiratory volume in one second; NO: nitric oxide; CO: carbon monoxide. [#]: 40 mg for 2 weeks.

The results of the present study demonstrate a reduced response to oral corticosteroids in smokers with asthma compared with never-smokers, measured by morning PEF, rescue medication use, daytime symptoms and asthma control score, but not by FEV1. This result was similar, but not identical, to findings in previous studies using inhaled fluticasone [6] or oral prednisolone [7] compared with a placebo. The current study was designed differently, with a single arm of treatment, and included smokers and never-smokers with baseline lung function more severe than in the present authors' previous studies.

Smoking is widely accepted as the major cause of COPD. It can often be difficult to differentiate smokers with asthma from those with COPD. However, the current authors are confident that the smokers in the present study had asthma rather than COPD. The smokers with asthma fulfilled the diagnostic criteria for asthma, had a mean age of 47 yrs and had been symptomatic from their mid-20s, which would be rare in patients with COPD. The asthmatic smokers had a post-salbutamol FEV1 of >75% pred, higher than expected in symptomatic patients with COPD, and had reversibility to salbutamol of ⩾15%. In a previous study, it was found that induced sputum neutrophil counts were elevated in smokers with asthma compared with nonsmokers with mild asthma [43]. In the current study, there was a trend towards a raised neutrophil count in the smoking asthmatics compared to the never-smokers (p=0.070), but both groups had more severe disease.

In conclusion, the results of the current study show that smokers with asthma have an impaired cutaneous vasoconstrictor response to topical corticosteroids compared with never-smokers with asthma. This finding suggests that the insensitivity to corticosteroids in smokers with asthma affects tissue sites other than the airways. This not only has implications for smokers with asthma, but may also be important in other corticosteroid-sensitive inflammatory conditions.

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